

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau

(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/005248 A1(51) International Patent Classification⁷: C07D 207/08, 207/09, 207/10, 401/12, A61K 31/40

Mark, G. [US/US]; 15 Orchard Street W, Califon, NJ 07830 (US). CHANDRAMOULI, Nagarajan [US/US]; 2 Symor Drive, Morristown, NJ 07960 (US). BAIR, Kenneth, Walter [US/US]; 95 Melrose Road, Mountain Lakes, NJ 07046 (US).

(21) International Application Number: PCT/EP2003/007005

(22) International Filing Date: 1 July 2003 (01.07.2003)

(74) Agent: GRUBB, Philip; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(25) Filing Language: English

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(26) Publication Language: English

(84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

(30) Priority Data: 60/393,150 2 July 2002 (02.07.2002) US

Published:
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

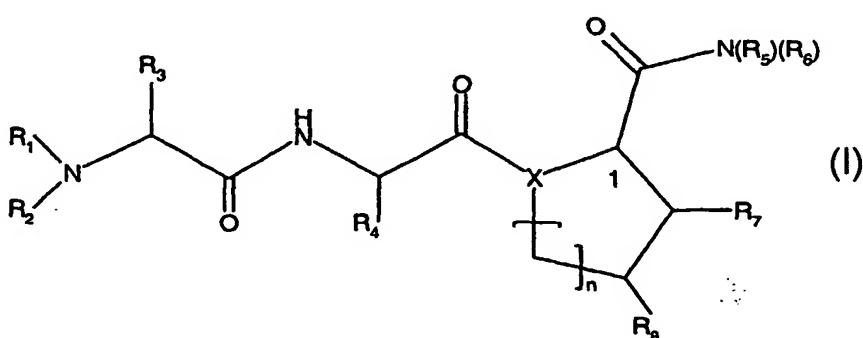
(71) Applicant (for all designated States except AT, US): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant (for AT only): NOVARTIS PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SHARMA, Sushil, Kumar [US/US]; 9 Bakley Terrace, West Orange, NJ 07052 (US). ZAWEL, Leigh [US/US]; 1861 Woodland Terrace, Bound Brook, NJ 08805 (US). PALERMO,

(54) Title: PEPTIDE INHIBITORS OF SMAC PROTEIN BINDING TO INHIBITOR OF APOPTOSIS PROTEINS (IAP)



(57) Abstract: The present disclosure relates to XIAP inhibitor compounds of the formula I (I) wherein the substituents are as described in the specification. The inventive compounds are useful as therapeutic agents for the treatment of proliferative disorders, including cancer.

WO 2004/005248 A1

INTERNATIONAL SEARCH REPORT

International Application No. . . .
PCT/EP 03/07005A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/08 C07D207/09 C07D207/10 C07D401/12 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EP0-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KIPP, RACHAEL A. ET AL: "Molecular Targeting of Inhibitor of Apoptosis Proteins Based on Small Molecule Mimics of Natural Binding Partners" BIOCHEMISTRY (2002), 41(23), 7344-7349 , XP000292287 table 1 summary & DATABASE CHEMABSPLUS 'Online! chemical abstracts service; abstract n°363320(2002), RN 402594-17-6</p> <p>—</p> <p>—/—</p>	1-16

 Further documents are listed in the continuation of box C Patent family members are listed in annex

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
23 October 2003	29/10/2003
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 91 651 epo nl, Fax: (+31-70) 340-3016	Samsam Bakhtiyari, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/07005

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WU, JIA-WEI ET AL: "Structural analysis of a functional DIAP1 fragment bound to grim and hid peptides" MOLECULAR CELL (2001), 8(1), 95-104 , XP009018631 table 1 figure 2 & DATABASE CHEMABSPLUS 'Online! chemical abstract service; abstract n°561493 (2001), RN 364604-50-2, RN 364604-53-5</p> <p>—</p>	1-16
P,X	<p>ARNT, CHRISTINA R. ET AL: "Synthetic Smac /DIABLO Peptides Enhance the Effects of Chemotherapeutic Agents by Binding XIAP and cIAP1 in Situ" JOURNAL OF BIOLOGICAL CHEMISTRY (2002), 277(46), 44236-44243 , XP001155278 page 44236 summary</p> <p>—</p>	1-16
A	<p>WO 01 15511 A (UNIV PITTSBURGH) 8 March 2001 (2001-03-08) the whole document</p> <p>—</p>	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/07005

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 11-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to compounds given in formula (I) in claim 1:

X= N
n=1
R4= i-Pr
R3 = Me
R2= alkyl

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/07005

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0115511	A 08-03-2001	AU 7473500 A		26-03-2001
		EP 1210362 A2		05-06-2002
		WO 0115511 A2		08-03-2001
		US 2003104622 A1		05-06-2003